DOI: 10.53469/jcmp.2026.08(03).54

The Role of Neuroimmune Interactions and Glial Cell Regulation in Pain-Depression Comorbidity

Xin Su[1], Haiguang Yuan[1,2,*]

[1]School of Acupuncture and Tuina, Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Department of Preventive Treatment of Disease, Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
Correspondence Author

Abstract: ***Pain and depression frequently co-occur in clinical settings, mutually exacerbating each other and forming a vicious cycle that significantly impairs patients' quality of life. However, the underlying mechanisms of this comorbidity remain incompletely understood. Traditional theories have primarily focused on aberrant neural circuits and monoaminergic neurotransmitter imbalances. Recent studies, however, suggest that the neuroimmune system—particularly glial cells within the central nervous system—plays a critical role in the onset and progression of pain–depression comorbidity. This review systematically summarizes advances in research on neuroimmune responses in pain–depression comorbidity, with a particular emphasis on glial cell–mediated dysregulation of central immune homeostasis. Our aim is to provide new insights into the pathophysiological mechanisms underlying this comorbidity and to lay a theoretical foundation for the development of novel therapeutic strategies.***

Keywords: Chronic pain, Depression, Comorbidity, Neuroimmune, Glial cells**.**

1. Introduction

Chronic pain and depression are both major global public health concerns, with a high rate of comorbidity. Epidemiological studies indicate that over 50% of patients with chronic pain exhibit significant depressive symptoms, while individuals with depression often experience various forms of somatic pain [1]. This comorbid condition not only substantially diminishes patients' quality of life but also complicates clinical management, imposing a considerable economic burden on society. Traditionally, research on pain–depression comorbidity has focused on shared neural circuits, such as the amygdala–anterior cingulate cortex pathway and the reward system [2,3], as well as dysregulation of neurotransmitter systems, including serotonergic and noradrenergic signaling [4]. However, these mechanisms are insufficient to fully account for the complex clinical manifestations observed in comorbid patients.

In recent years, neuroimmune mechanisms have garnered increasing attention as a critical bridge linking somatosensory and emotional regulation. Neuroimmune interactions occur not only in the periphery but also exert profound effects on central nervous system (CNS) function. Microglia and astrocytes, the principal immune cells in the CNS, exhibit sustained activation in animal models of both chronic pain and depression [5,6]. Activated glial cells release a wide array of pro-inflammatory cytokines and neuroactive substances, which collectively contribute to the pathophysiology of pain–depression comorbidity by modulating synaptic transmission, inhibiting neurogenesis, and inducing oxidative stress [7,8].

Building upon traditional neurobiological frameworks, this review focuses on the pivotal role of neuroimmune interactions and glial cells in the transition from peripheral immune activation to central immune dysregulation. We also systematically summarize relevant therapeutic strategies, aiming to provide a reference for further research and clinical translation in this field.

2. Activation and Propagation of Neuroimmune Responses

Neuroimmune abnormalities in pain–depression comorbidity are often triggered by peripheral tissue injury or psychological stress. Evidence indicates the existence of a "peripheral–central immune dialogue" that connects the somatosensory system with central circuits involved in emotional regulation. In chronic pain conditions, including neuropathic pain, inflammatory pain, and bone cancer pain, the peripheral immune system is initially activated. Subsequently, inflammatory signals are transmitted to the central nervous system (CNS) via both circulatory and neural pathways, compromising blood–brain barrier (BBB) integrity, activating central immune responses, and ultimately contributing to pain hypersensitivity and depression-like behaviors.

2.1 Peripheral Nerve Injury and Initial Immune Response

In neuropathic pain models, such as chronic constriction injury of the sciatic nerve or spinal nerve ligation, damaged neurons release signaling molecules including ATP and chemokines, which recruit and activate peripheral immune cells as well as satellite glial cells in the dorsal root ganglia [9]. These cells produce pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), which enhance the excitability of nociceptive neurons and exacerbate pain transmission. In addition, these inflammatory signals can reach the CNS via the circulation or vagal pathways, triggering central immune responses.

2.2 Blood-Brain Barrier Permeability and Central Immune Activation

Chronic peripheral inflammation and stress can impair the integrity of the BBB, increasing its permeability and facilitating the entry of peripherally derived inflammatory mediators into the CNS. These mediators can directly act on

brain vascular endothelial cells and glial cells, initiating central immune responses [10]. Simultaneously, resident microglia within the CNS can detect peripheral inflammatory signals and rapidly enter an activated state, further amplifying central inflammatory processes.

3. Roles of Glial Cells in Central Immunity

Glial cells are key immune regulatory cells in the central nervous system (CNS), playing a central role in maintaining neural homeostasis and modulating inflammatory responses. Microglia, as the resident immune cells of the CNS, can recognize pathogens, damage-associated signals, and apoptotic cells, and maintain microenvironmental stability through phagocytosis and clearance. Under pathological conditions, microglia can polarize into pro-inflammatory or anti-inflammatory phenotypes, secreting cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), thereby regulating local inflammatory responses. Astrocytes contribute to immune cell recruitment and activation through the secretion of cytokines and chemokines, and participate in blood–brain barrier (BBB) formation and maintenance, limiting excessive infiltration of peripheral immune cells. In states of neural injury or disease, astrocytes also exert neuroprotective effects by releasing antioxidant molecules and providing metabolic support. Oligodendrocytes are primarily responsible for myelin formation and maintenance, and in inflammatory or injury contexts, they can secrete inflammation-related molecules, contributing to myelin repair and neural function restoration. Collectively, glial cells act as a bridge in pain–depression comorbidity by detecting pathological signals, regulating inflammatory responses, providing neuroprotection, and promoting repair.

3.1 Microglial Polarization and Synaptic Remodeling

Microglia are the intrinsic immune cells of the CNS and the only resident immune cells derived from the myeloid lineage. In pain–depression comorbidity models, microglia predominantly polarize toward the pro-inflammatory M1 phenotype, releasing IL-1β, TNF-α, and IL-6, which directly enhance neuronal excitability and suppress the expression of key molecules such as brain-derived neurotrophic factor (BDNF), thereby promoting depression-like behaviors [11,12]. Recent studies have further shown that in mice with chronic pain comorbid with anxiety and depression, microglia in the medial prefrontal cortex exhibit enhanced phagocytosis of the excitatory postsynaptic marker PSD-95, a process dependent on the MERTK receptor, leading to synaptic loss and potentially underlying cognitive and emotional deficits in the comorbid state [13]. Multiple studies [11,14,15] also indicate that microglia-specific signaling pathways, including P2X7 receptor-mediated NLRP3 inflammasome activation, the cGAS–STING pathway, and JAK/STAT3-mediated Th17 cell differentiation, play key roles in the pathogenesis of comorbidity.

3.2 Astrocyte Dysfunction and Neurotransmitter Imbalance

Astrocytes are the most abundant glial cell type in the CNS, contributing under physiological conditions to neuronal support, BBB regulation, synaptic function, and immune repair. Under pathological conditions, astrocytes exhibit impaired glutamate cycling and reduced neurotrophic support. Reactive astrocytes show decreased glutamate uptake, resulting in extracellular glutamate accumulation, excitotoxicity, and disrupted synaptic plasticity. Excitation/inhibition imbalance in the anterior cingulate cortex is a shared feature of chronic pain and negative emotional states [16]. Additionally, astrocytes are an important source of BDNF, and reduced BDNF secretion in comorbid states not only affects neuronal survival, differentiation, and synaptic plasticity but also correlates with impaired hippocampal neurogenesis and depression-like behaviors [17].

3.3 Oligodendrocytes and Myelin Damage

Oligodendrocytes are the myelinating cells of the CNS, responsible for axonal myelination and maintenance, providing metabolic support, and contributing to neural development and repair. Recent research has begun to explore the role of white matter and myelin in chronic pain–depression comorbidity. Studies indicate that activation of the basal lateral amygdala–anterior cingulate cortex pathway is sufficient to induce depression-like behaviors, accompanied by significant downregulation of myelin formation and oligodendrocyte lineage-related genes, suggesting that myelin damage may represent a novel mechanism underlying emotional dysregulation. Further investigations reveal that semaphorin 4a (Sema4a) is markedly upregulated in this context and is necessary for the development of emotional dysfunction. Moreover, oligodendrocytes and their precursor cells are highly sensitive to neuroinflammatory environments; pro-inflammatory cytokines can directly inhibit oligodendrocyte differentiation and myelin regeneration, while also inducing oxidative stress and ferroptosis, further compromising myelin integrity [18]. These findings provide a new perspective on the role of oligodendrocyte-mediated myelin remodeling in emotional regulation.

4. Emerging Comorbidity Mechanisms: Regulated Cell Death

Beyond classical inflammatory pathways, recent studies indicate that ferroptosis, mitochondrial dysfunction, autophagy, and complement system–mediated neuroimmune interactions also play important roles in the development of pain–depression comorbidity, acting as critical bridges between neuroinflammation and neuronal damage.

4.1 Ferroptosis

Ferroptosis is an iron-dependent, regulated form of cell death characterized by the accumulation of lipid peroxides. In comorbidity models, typical markers of ferroptosis have been observed in the hippocampus and spinal cord, including

downregulation of glutathione peroxidase 4 (GPX4) and xCT, upregulation of acyl-CoA synthetase long-chain family member 4 (ACSL4) and lipoxygenases (LOX), increased levels of lipid peroxidation products such as malondialdehyde (MDA), and disruption of mitochondrial cristae structure [19,20]. Studies show that ferroptosis inhibitors or electroacupuncture interventions can modulate iron metabolism and antioxidant systems, significantly alleviating pain and depression-like behaviors, suggesting a causal role of ferroptosis in comorbidity [21]. Notably, aberrant activation of microglia and astrocytes is a major trigger of CNS ferroptosis; pro-inflammatory factors released by activated glial cells reduce GPX4 expression in neurons and oligodendrocytes, while microglia themselves can undergo ferroptosis, further exacerbating neuroinflammation [14].

4.2 Mitochondrial Dysfunction and Autophagy

Mitochondrial dysfunction is a shared pathological basis of neurodegenerative and psychiatric disorders. In comorbidity models, hippocampal and periaqueductal gray neurons exhibit decreased mitochondrial membrane potential, reduced ATP production, and excessive reactive oxygen species (ROS) generation [22,23]. Studies demonstrate that puerarin can bind to Bax protein to improve mitochondrial function and alleviate comorbidity symptoms [22]. Moreover, dysregulation of mitophagy-related pathways, such as PINK1/Parkin, is implicated in the progression of comorbidity. Research indicates that the “Shugan Tiaoxin” acupuncture protocol enhances mitophagy to clear damaged mitochondria, thereby exerting neuroprotective effects [24].

4.3 Complement System

The complement system is a critical component of innate immunity, recognizing and clearing pathogens through cascade activation, regulating inflammatory responses, and participating in both innate and adaptive immunity. Studies have found that complement proteins C1q, C3, and their receptors are upregulated in the amygdala and hippocampus of comorbidity models, potentially contributing to pain and depression via microglia-dependent synaptic pruning. Complement-mediated synaptic remodeling is primarily executed by microglia; in comorbid states, upregulation of complement proteins such as C1q and C3 activates microglial phagocytic function, leading to excessive removal of excitatory synapses. This process is particularly pronounced in brain regions associated with emotion and cognition, including the medial prefrontal cortex and hippocampus [8].

5. Novel Therapeutic Strategies Targeting Neuroimmune Interactions and Glial Cells

5.1 Pharmacological Interventions

In recent years, targeted therapies addressing key mechanisms of comorbidity, such as neuroimmune dysregulation and oxidative stress, have emerged. The soluble epoxide hydrolase (sEH) inhibitor TPPU significantly reduces systemic and central nervous system inflammation via the AHR/TSPO signaling pathway and effectively ameliorates anhedonia-like behavior in chronic pain models [25]. Dexmedetomidine, a highly selective α2-adrenoceptor agonist, has been shown to reduce postoperative pain and anxiety/depressive symptoms when administered intraoperatively to chronic pain patients with comorbid anxiety and depression, highlighting its potential as an adjunctive therapy [26]. Natural compounds are also attracting attention due to their multi-target properties and low toxicity. For example, puerarin improves mitochondrial function by targeting Bax protein [22]; gallic acid blocks P2X7 receptor–mediated ferroptosis [14]; the spiro- piperazine derivative DXL-A-24 activates the Nrf2/ARE antioxidant pathway [27]; and isorhamnetin exerts neuroprotective, antidepressant, and analgesic effects in animal models via antioxidant, anti-inflammatory, and monoaminergic mechanisms [28]. Moreover, classical drugs have been found to possess additional mechanisms of action; for instance, the antidepressant vortioxetine’s analgesic effect is closely associated with inhibition of microglial marker IBA-1 and related neuroinflammatory pathways [29]. These findings suggest that multi-target pharmacological interventions aimed at neuroimmune regulation and glial cells hold therapeutic potential for pain–depression comorbidity.

5.2 Non-Pharmacological Interventions

Both electroacupuncture and manual therapies have demonstrated beneficial effects in preclinical and clinical studies. Electroacupuncture has been shown to inhibit microglial activation and M1 polarization in the spinal cord and brain, promoting a shift toward the anti-inflammatory M2 phenotype, a process closely associated with suppression of cGAS–STING and NLRP3 pathways [15]. It also increases the Bcl-2/Bax ratio, reduces Cyt-C and Caspase-9 expression, and decreases neuronal apoptosis [30]. Additionally, electroacupuncture activates the Nrf2 pathway, upregulating GPX4 and FTH1, thereby effectively inhibiting hippocampal neuronal ferroptosis [21]; it also modulates the GABAergic system, restores glutamate balance, and exerts analgesic and antidepressant effects by normalizing aberrant functional connectivity in brain regions such as the amygdala [31]. Manual therapies improve hippocampal neuronal structural plasticity and alleviate depression-like behaviors associated with neuropathic pain via the SIRT1/BDNF/TrkB signaling pathway [32]. Environmental enrichment interventions have also been shown to prevent pain hypersensitivity and depression-like behaviors in neuropathic pain model mice through multimodal sensory, physical, and social stimulation, potentially by inhibiting neuroinflammation and enhancing neurotrophic factor expression [33]. Furthermore, perioperative psychological interventions based on social-cognitive theory have demonstrated significant efficacy in alleviating pain, anxiety, and depressive symptoms in patients [34].

6. Conclusion and Outlook

This review systematically summarized the critical roles of neuroimmune responses and glial cells in pain–depression comorbidity, highlighting the complex pathological network formed from peripheral immune activation to sustained central glia-mediated neuroinflammation. This network ultimately disrupts both pain and emotional regulation through mechanisms such as altered synaptic plasticity, oxidative stress induction, novel forms of cell death, and

impaired neurogenesis.

Despite significant advances, many key questions remain unresolved. Mechanistically, further studies are needed to delineate the precise regulatory roles of specific neural circuits in comorbidity. Moreover, future preclinical research should incorporate both male and female animal models to clarify sex-dependent differences in glial cell responses and circuit regulation, providing a foundation for precision medicine. Translationally, the development of reliable biomarkers represents a crucial step toward accurate diagnosis and individualized treatment, with peripheral inflammatory mediators and CNS-specific molecules showing potential for diagnostic and therapeutic efficacy assessment in comorbid patients. Additionally, randomized controlled trials evaluating the combined application of physical therapies, such as electroacupuncture and manual therapy, with neuroimmune-targeted pharmacological interventions are warranted to systematically assess their synergistic effects and safety.

In summary, targeting neuroimmune mechanisms and glial cells offers a novel framework for understanding and managing pain–depression comorbidity. Such approaches hold promise for the development of dual-action therapies capable of simultaneously alleviating both pain and emotional symptoms, providing new therapeutic hope for patients suffering from this challenging comorbid condition.

References

[1] Wang X, Shu Q. Advances in the study of neural mechanisms and comprehensive intervention strategies for chronic pain and negative emotions. J Sun Yat-Sen Univ Med Sci, 2025, 46(2): 197-209.

[2] Ma C, Ye Y, Yan X. Progress in amygdala-mediated pain-emotion neural circuits. J Shanghai Jiao Tong Univ Med Sci, 2023, 43(10): 1304-1310.

[3] Zeng S, Wu D, Xie L, et al. Changes in negative emotions induced by chronic pain and related brain circuits. J Neurol Anat, 2023, 39(1): 111-114.

[4] Zhao J, Xie J. Pharmacological treatment of depression and chronic pain. Med Herald, 2019, 38(5): 622-625.

[5] Yue L, Xiong Y. Role of glial cells in neuropathic pain and depression comorbidity. Chin J Pain Med, 2024, 30(6): 407-412.

[6] Lopes F, Vicentini FA, Cluny NL, et al. Brain TNF drives post-inflammation depression-like behavior and persistent pain in experimental arthritis. Brain Behav Immun, 2020, 89: 224-232.

[7] Huang Z, Sun J, Li H, et al. Microglial-derived nitric oxide regulates amygdala synaptic plasticity to drive chronic pain and depression induced by lumbar disc herniation. Neuropharmacology, 2025, 280: 110662.

[8] Tang S, Hu W, Zou H, et al. The complement system: A potential target for the comorbidity of chronic pain and depression. Korean J Pain, 2024, 37(2): 91-106.

[9] Xu X, Chen R, Yu Y, et al. Pulsed radiofrequency on DRG inhibits hippocampal neuroinflammation by regulating spinal GRK2/p38 expression and enhances spinal autophagy to reduce pain and depression in male rats with spared nerve injury. Int Immunopharmacol, 2024, 127: 111419.

[10] Jiang R, Geha P, Rosenblatt M, et al. The inflammatory and genetic mechanisms underlying the cumulative effect of co-occurring pain conditions on depression. Sci Adv, 2025, 11(14): eadt1083.

[11] Wu S, Jiang J, Wang D, et al. JAK/STAT3 signaling promotes pain and depression-like behaviors in rats with bone cancer pain by regulating Th17 cell differentiation. Brain Res Bull, 2025, 221: 111218.

[12] Liu L, Xu H, Ji K, et al. Dynamic changes of BDNF/TrkB/CREB signaling in the brains of mice with neuropathic pain-induced depression. J Med Grad, 2022, 35(11): 1132-1137.

[13] Li W, Chang W, Cui K, et al. Electroacupuncture reduces microglial hyperactivity and synaptic phagocytosis in the medial prefrontal cortex to treat chronic pain comorbid with anxiety and depression. Brain Res Bull, 2025, 230: 111521.

[14] Yang R, Shi L, Si H, et al. Gallic acid improves comorbid chronic pain and depression behaviors by inhibiting P2X7 receptor-mediated ferroptosis in the spinal cord of rats. ACS Chem Neurosci, 2023, 14(4): 667-676.

[15] Xin H, Zou J, Le W. Electroacupuncture affects microglia-mediated postherpetic neuralgia via the cGAS-STING pathway. J Chin Med Univ, 2025, 54(3): 208-213, 218.

[16] Wang TZ, Wang F, Tian ZC, et al. Cingulate cGMP-dependent protein kinase I facilitates chronic pain and pain-related anxiety and depression. Pain, 2023, 164(11): 2447-2462.

[17] Li S, Huang JP, Luo D, et al. Effects of electroacupuncture on hippocampal AcH3/BDNF in SNI-induced pain-depression model rats. J Sun Yat-Sen Univ Med Sci, 2023, 44(1): 44-50.

[18] Becker LJ, Fillinger C, Waegaert R, et al. The basolateral amygdala-anterior cingulate pathway contributes to depression-like behaviors and comorbidity with chronic pain behaviors in male mice. Nat Commun, 2023, 14(1): 2198.

[19] Li YN, Xue CC, Wang KQ. Correlation analysis of hippocampal ferroptosis and neuropathic pain-induced mood disorders in CCI rats. J Chongqing Med Univ, 2025, 50(5): 630-639.

[20] Liu G, Liu D, Shi D, et al. Electroacupuncture ameliorates chronic inflammatory pain and depression comorbidity by inhibiting Nrf2-mediated ferroptosis in hippocampal neurons. Neurochem Res, 2025, 50(3): 149.

[21] Liu GH, Shi DL, Wang ZH, et al. Mechanistic study of “Shugan Tiaoshen” acupuncture regulating hippocampal neuronal ferroptosis to improve chronic inflammatory pain and depression comorbidity. Acupunct Res, 2024 [2025-10-22].

[22] Sheng G, Wu Y, Yao L, et al. Puerarin improves the comorbidity of chronic pain and depression by binding with Bax and reducing mitochondrial dysfunction. Mol Pain, 2025, 21: 17448069251335230.

[23] Yang P, Chen H, Wang T, et al. Electroacupuncture attenuates chronic inflammatory pain and depression comorbidity by inhibiting hippocampal neuronal apoptosis via the PI3K/AKT signaling pathway. Neurosci Lett, 2023, 812: 137411.

[24] Liu GH, Fu W, Wu YS, et al. “Shugan Tiaoshen” acupuncture regulates PINK1/Parkin-mediated hippocampal neuronal mitophagy to improve chronic inflammatory pain and depression comorbidity. Chin Acupunct, 2025 [2025-10-22].
[25] The soluble epoxide hydrolase inhibitor TPPU improves comorbidity of chronic pain and depression via the AHR and TSPO signaling. [2025-10-23].
[26] Ren Y, Huang P, Jin X. Dexmedetomidine for chronic pain patients with anxiety and depression: A propensity score matching cohort study. BMC Anesthesiol, 2025, 25(1): 222.
[27] Liu DG, Xu Y, Zhao W, et al. Effects of spiro-piperazine compound DXL-A-24 on behavior and antioxidant capacity in rats with chronic pain-depression comorbidity. J Clin Anesth, 2025, 41(8): 851-858.
[28] Alqudah A, Qnais E, Bsieso Y, et al. Neuroprotective and antidepressant effects of isorhamnetin: Mechanistic evaluations in a reserpine-induced mouse model of pain and depression. Mol Neurobiol, 2025.
[29] Ran YH, Wang YX, Shi LM, et al. Analgesic effects and potential mechanisms of the antidepressant vilazodone. Chin J Pharmacol Toxicol, 2025, 39(7): 481-488.
[30] Yang P, Su SY, Wang T. Effects of electroacupuncture on hippocampal Cyt-C and caspase-9 expression in rats with chronic pain-depression comorbidity. Chin J Inf Tradit Chin Med, 2024, 31(3): 85-91.
[31] Yin X, Zeng XL, Lin JJ, et al. Brain functional changes following electroacupuncture in a mouse model of comorbid pain and depression: A resting-state fMRI study. J Integr Med, 2025, 23(2): 159-168.
[32] Wang XH, Lin ZG, Chen SJ, et al. Effects of tuina on neuropathic pain and depression-like behavior in rats via the SIRT1/BDNF/TrkB signaling pathway. Chin J Inf Tradit Chin Med, 2025, 32(3): 89-97.
[33] Medeiros P, Medeiros AC, De Freitas RL, et al. Enriched environment prevents hypernociception and depression-like behavior in a psychiatric disorder and neuropathic pain comorbidity experimental condition. Physiol Behav, 2025, 291: 114795.
[34] Mao HJ, Wang LF, Lin C. Psychological intervention based on social cognitive theory: Treating pain, anxiety, and depression in perioperative patients. World J Psychiatry, 2024, 14(8): 1199-1207.